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APPLICATION NUMBER: *60/525,430*
FILING DATE: *November 26, 2003*
RELATED PCT APPLICATION NUMBER: *PCT/US04/39728*

Certified by

Jon W Dudas

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PTO/SB/16 (08-03)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Congxin	Liang	Sunnyvale, California

Additional inventors are being named on the 0 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Hydroxy Carboxy Pyrrolyl-indolinone Derivatives as Protein Kinase Inhibitors

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☐ Customer Number:

OR

☑ Firm or Individual Name	Congxin Liang				
Address	729 West Remington Drive				
Address					
City	Sunnyvale	State	CA	Zip	94087
Country	USA	Telephone	408-746-0486	Fax	408-746-0486

ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 10 ☐ CD(s), Number

☐ Drawing(s) *Number of Sheets* ☑ Other (specify) Cover letter

☐ Application Date Sheet. See 37 CFR 1.76

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☑ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees.

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,

SIGNATURE Congxin Liang

TYPED or PRINTED NAME Congxin Liang

TELEPHONE 408-746-0486

Date NOV. 25, 2003

REGISTRATION NO. *(if appropriate)*

Docket Number:

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

16638 U.S. PTO 112603

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☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 80.00

Complete if Known	
Application Number	
Filing Date	NOV. 25, 2003
First Named Inventor	CONGXIN LIANG
Examiner Name	
Art Unit	
Attorney Docket No.	

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☒ Credit card ☐ Money Order ☐ Other ☐ None

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	80.00

SUBTOTAL (1) ($) 80.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below	Fee Paid
Total Claims		-20** =	X	=
Independent Claims		- 3** =	X	=
Multiple Dependent				=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

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FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid **SUBTOTAL (3)** ($)

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	CONGXIN LIANG	*Registration No. (Attorney/Agent)*		*Telephone*	408-746-0486
Signature	Congxin Liang			*Date*	NOV. 25, 2003

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Nov. 25, 2003

Congxin Liang
729 W. Remington Dr.
Sunnyvale, CA 94087
(408)-746-0486
chrisliang03@yahoo.com

Mail Stop Provisional Patent Application
Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

Enclosed please find the following documents for a provisional patent application:

- Provisional Application for Patent Cover Sheet
- Fee transmittal for FY 2004
- Credit card payment form (for $80.00)
- Description of the invention: Hydroxy Carboxy Pyrrolyl-indolinone Derivatives as Protein Kinase Inhibitors (10 pages)

Please check the list and call me at (408)-718-9689 (mobile) if the application is incomplete.

Best regards,

Congxin Liang

HYDROXY CARBOXY PYRROLYL-INDOLINONE DERIVATIVES AS PROTEIN KINASE INHIBITORS

BACKGROUND OF THE INVENTION

Field of Invention

This invention relates to certain hydroxy carboxy pyrrolyl-indolinone derivatives and their pharmaceutically acceptable salts as protein kinase inhibitors. The compounds of this invention are therefore useful in treating disorders related to abnormal protein kinase activities such as cancer.

State of the Art

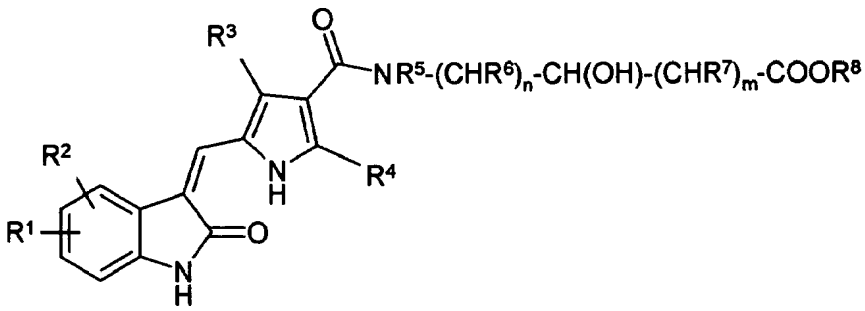
Protein kinases are enzymes that catalyze the phosphorylation of hydroxyl groups of tyrosine, serine, and threonine residues of proteins. Many aspects of cell life (for example, cell growth, differentiation, proliferation, cell cycle and survival) depend on protein kinase activities. Furthermore, abnormal protein kinase activity has been related to a host of disorders such as cancer and inflammation. Therefore, there is a great deal of effort directed to identifying ways to modulate protein kinase activities. In particular, many attempts have been made to identify small molecules which act as protein kinase inhibitors.

DESCRIPTION OF THE INVENTION

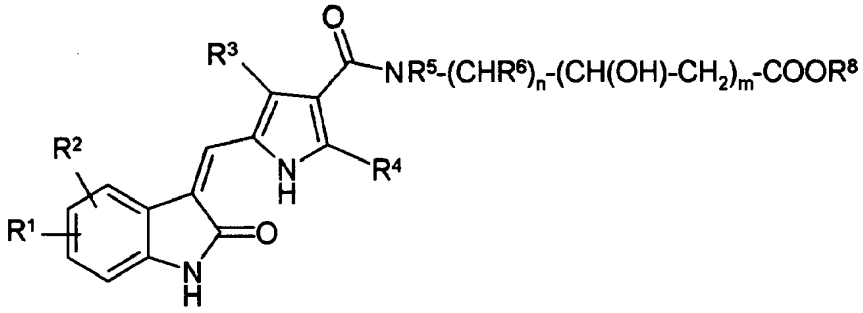
This invention discloses that certain hydroxy carboxy pyrrolyl-indolinone derivatives may have interesting and unexpected properties that advantageously distinguish them from known compounds. They are therefore useful in treating disorders related to abnormal protein kinase activities such as cancer.

One embodiment of this invention is a compound of Formula (I) or (II):

(I)



(II)



wherein:

R^1 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, amino, alkylamino, amide;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, amino, alkylamino, amide, aryl, heteroaryl, sulfonyl, sulfonamide;

R^3 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and amide;

R^4 is selected from the group consisting of hydrogen, alkyl;

R^5 and R^6 are independently hydrogen or alkyl;

R^7 is hydrogen, alkyl or hydroxyl;

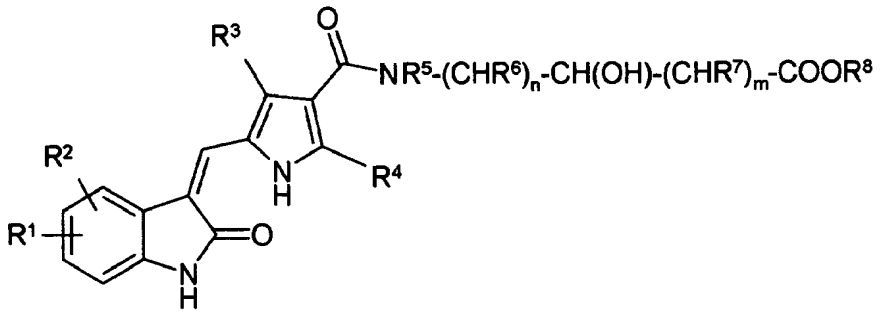
R^8 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted alkyl;

n and m are independently 0, 1, 2, or 3;

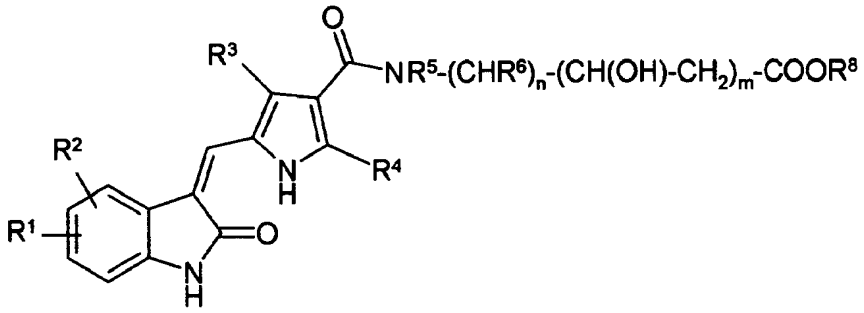
or a pharmaceutically acceptable salt, prodrug thereof. It may also act as a prodrug. The compound of Formula (I) or (II) may exist in or co-exist with its cyclic lactone form in solution or *in vivo*.

Another embodiment of this invention is a compound of Formula (**Ia**) or (**IIa**):

(Ia)



(IIa)



wherein:

R^1 and R^2 are independently hydrogen or fluoro and are located, respectively, at the 4- or 5-position of the indolinone ring;

R^3 and R^4 are methyl;

R^5, R^6, and R^8 are hydrogen;

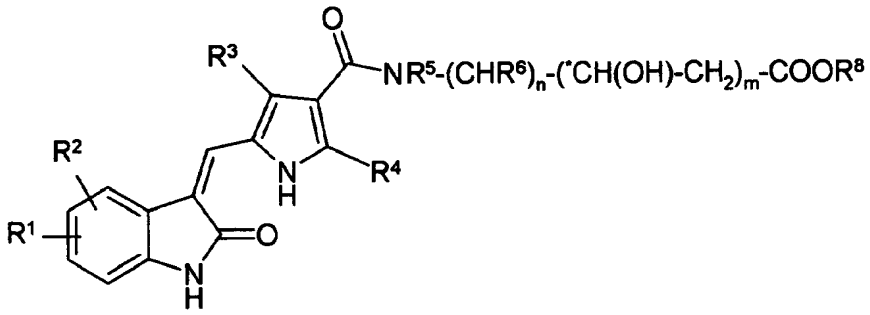
R^7 is hydrogen or hydroxyl;

n and m are independently 1, or 2;

or a pharmaceutically acceptable salt thereof. It may also act as a prodrug. The compound of Formula (**Ia**) or (**IIa**) may exist in or co-exist with its cyclic lactone form in solution or *in vivo*.

Another embodiment of this invention is a compound of Formula (**IIb**):

(IIb)



wherein:

R^1 and R^2 are independently hydrogen or fluoro and are located, respectively, at the 4- or 5-position of the indolinone ring;

R^3 and R^4 are methyl;

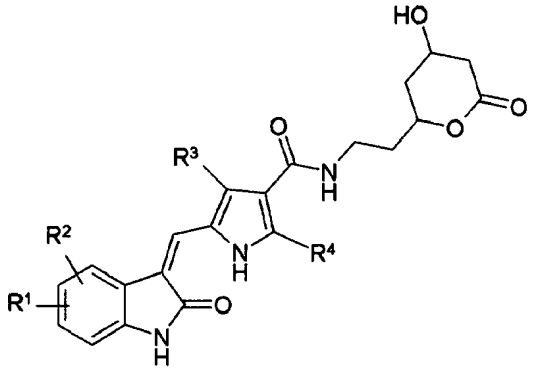
R^5, R^6, and R^8 are hydrogen;

n and m are 2;

or a pharmaceutically acceptable salt thereof. It may also act as a prodrug. Preferably, the stereochemistry at the *C is (*R*).

The compound of Formula (**IIb**) may exist in or co-exist with its cyclic lactone form with Formula (**IIc**) in solution or *in vivo*:

(IIc)

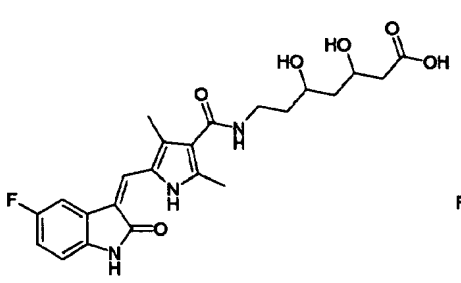


wherein:

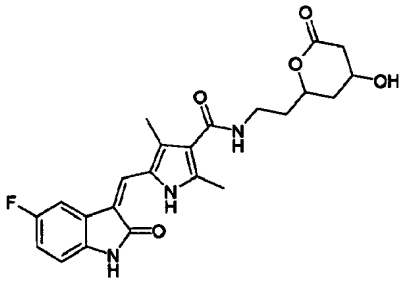
R^1 and R^2 are independently hydrogen or fluoro and are located, respectively, at the 4- or 5-position of the indolinone ring;

R^3 and R^4 are methyl.

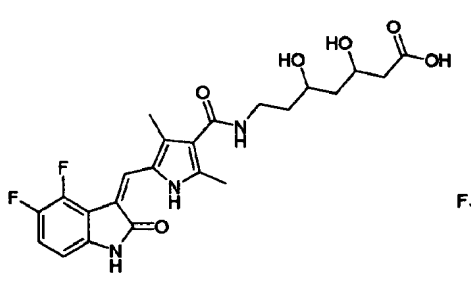
Representative compounds of the present invention are shown below.



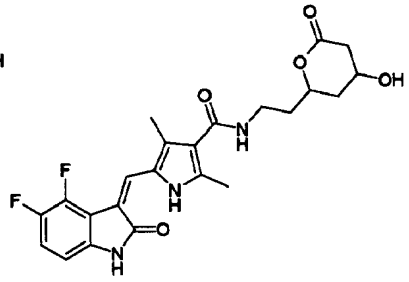
1



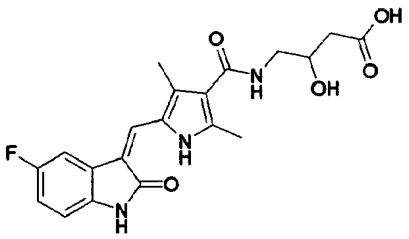
1a



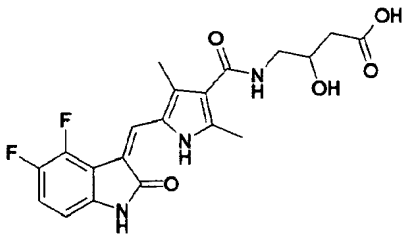
2



2a



3



4

In the above examples, **1a** is the cyclic lactone of **1** and they may co-exist in solution or *in vivo*. Similarly, **2a** is the cyclic lactone of **2** and they may co-exist in solution or *in vivo*. Furthermore, in the above examples the stereochemistry at the carbon atom carrying a hydroxyl group is either *RS*, *R*, or *S*. In **1**, **1a**, **2**, and **2a**, such stereochemistry is preferably *R*.

Utility

The present invention provides compounds capable of regulating and/or modulating protein kinase activities of, but not limited to, VEGFR and/or PDGFR. Thus, the present invention provides a therapeutic approach to the treatment of disorders related to the abnormal functioning of these kinases. Such disorders include, but not limited to,

solid tumors such as glioblastoma, melanoma, and Kaposi's sarcoma, and ovarian, lung, prostate, pancreatic, colon and epidermoid carcinoma. In addition, VEGFR/PDGFR inhibitors may also be used in the treatment of restenosis and diabetic retinopathy.

Furthermore, this invention relates to the inhibition of vasculogenesis and angiogenesis by receptor-mediated pathways, including the pathways comprising VEGF receptors, and/or PDGF receptors. Thus the present invention provides therapeutic approaches to the treatment of cancer and other diseases which involve the uncontrolled formation of blood vessels.

Synthesis of Compounds

The compounds of this invention can be synthesized by following the published general procedures (e.g. Sun et al., 2003, J. Med. Chem., 46:1116-119). But the following intermediates are specific to compounds of this invention and may be used in place of their respective counterparts in the above-mentioned general procedure: 4,5-difluoro-oxindole; (4*R*,6*R*)-*t*-butyl-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate; and 4-amino-3-hydroxy-butanic acid. These intermediates may be purchased from commercial sources (e.g. Fisher Scientific, Fairlawn, New Jersey). Another variation from the above-mentioned general procedure is that in the synthesis of **1/1a** and **2/2a** using (4*R*,6*R*)-*t*-butyl-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate, the protecting groups need to be removed from the final product. Yet another variation from the above-mentioned general procedure is that in the synthesis of **3** and **4** using 4-amino-3-hydroxy-butanic acid, the acid needs to be protected before amidation and the protection group needs to be removed from the final product. These variations from the above-mentioned general procedure can be understood and carried out by those skilled in the art. Thus, the compounds of the present invention can be synthesized by those skilled in the art.

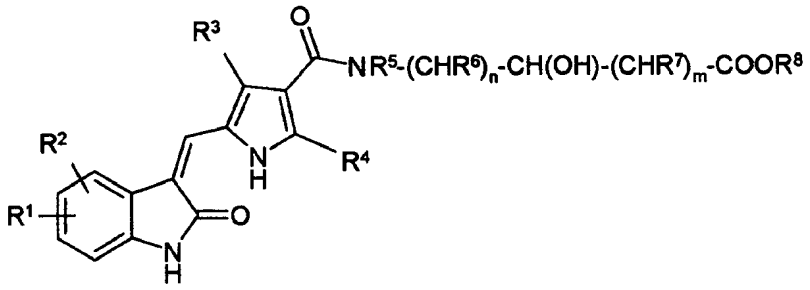
The compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

The Claims

What is claimed is:

1. A compound of Formula (**I**):

(**I**)



wherein:

R^1 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, amino, alkylamino, amide;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, amino, alkylamino, amide, aryl, heteroaryl, sulfonyl, sulfonamide;

R^3 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and amide;

R^4 is selected from the group consisting of hydrogen, alkyl;

R^5 and R^6 are independently hydrogen or alkyl;

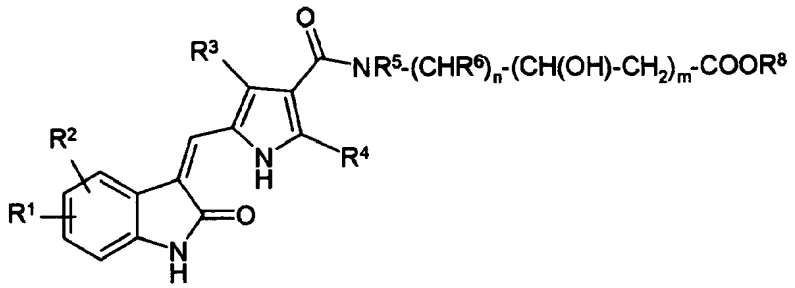
R^7 is hydrogen, alkyl, or hydroxyl;

R^8 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted alkyl;

n and m are independently 0, 1, 2, or 3;

or a pharmaceutically acceptable salt, prodrug thereof.

2. A compound of Formula (**II**):

(II) 

wherein:

R^1 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, amino, alkylamino, amide;

R^2 is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, haloalkyl, hydroxy, alkoxy, amino, alkylamino, amide, aryl, heteroaryl, sulfonyl, sulfonamide;

R^3 is selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, and amide;

R^4 is selected from the group consisting of hydrogen, alkyl;

R^5 and R^6 are independently hydrogen or alkyl;

R^8 is selected from the group consisting of hydrogen, alkyl, cycloalkyl, substituted alkyl;

n and m are independently 0, 1, 2, or 3;

or a pharmaceutically acceptable salt, prodrug thereof.

3. The compound of claim 1, wherein:

R^1 and R^2 are independently hydrogen or fluoro and are located, respectively, at the 4- or 5-position of the indolinone ring;

R^3 and R^4 are methyl;

R^5, R^6, R^7 and R^8 are hydrogen;

n and m are independently 0, 1, or 2;

or a pharmaceutically acceptable salt thereof.

4. The compound of claim 2, wherein:

R^1 and R^2 are independently hydrogen or fluoro and are located, respectively, at the 4- or 5-position of the indolinone ring;

R^3 and R^4 are methyl;

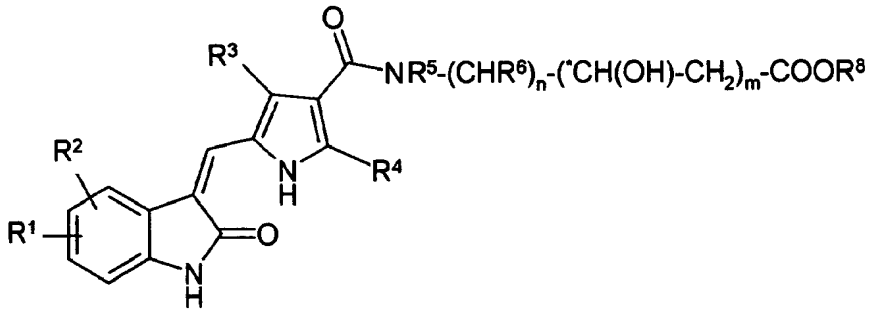
R^5, R^6, and R^8 are hydrogen;

n and m are independently 1, or 2;

or a pharmaceutically acceptable salt thereof.

5. A compound of Formula (**IIb**):

(IIb)



wherein:

R^1 and R^2 are independently hydrogen or fluoro and are located, respectively, at the 4- or 5-position of the indolinone ring;

R^3 and R^4 are methyl;

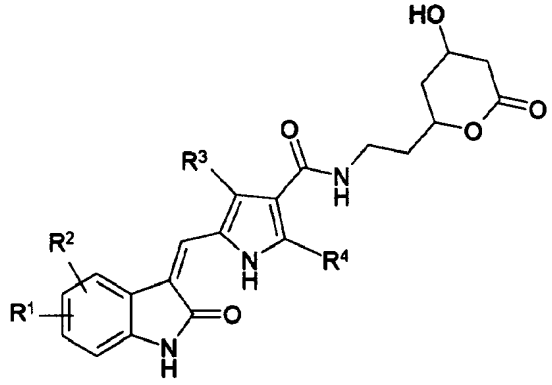
R^5, R^6, and R^8 are hydrogen;

n and m are 2;

or a pharmaceutically acceptable salt thereof.

6. A compound of Formula (**IIc**):

(IIc)

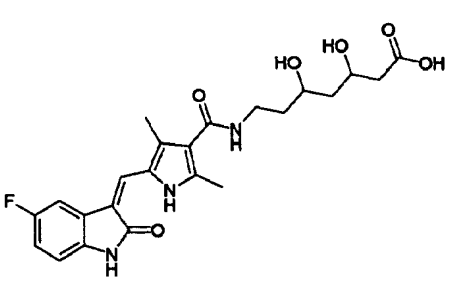


wherein:

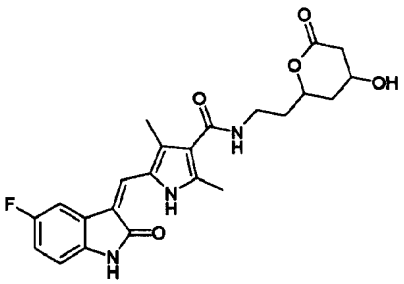
R^1 and R^2 are independently hydrogen or fluoro and are located, respectively, at the 4- or 5-position of the indolinone ring;

R^3 and R^4 are methyl.

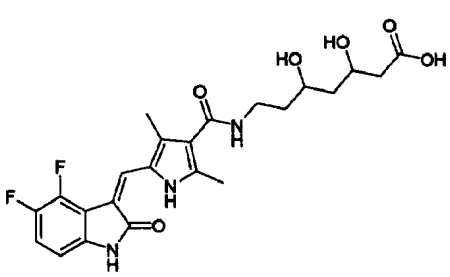
7. The compound or salt of claim 2, wherein the compound is selected from the group consisting of:



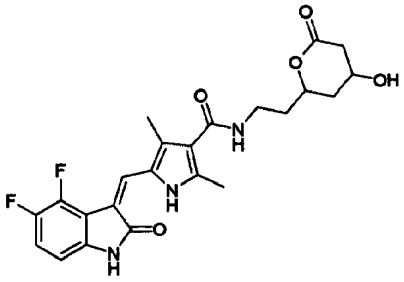
1



1a

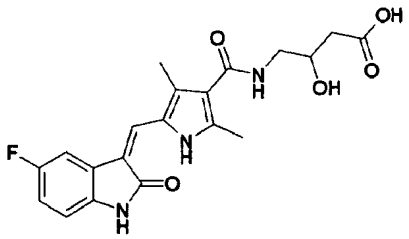


2

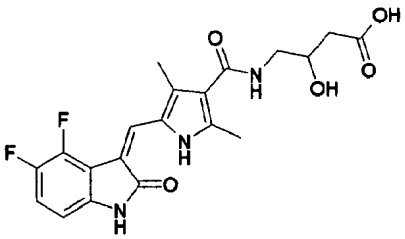


2a

8. The compound or salt of claim 1, wherein the compound is selected from the group consisting of:



3



4

9. A method for the modulation of the catalytic activity of a protein kinase with a compound or salt of any one of claims 1, 2, 3, 4, 5, 6, 7, or 8.

10. The method of claim 9, wherein said protein kinase is selected from the group consisting of VEGF receptors, PDGF receptors.